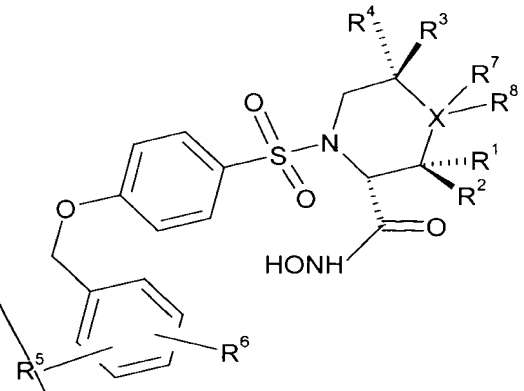
 EXPRESS MAIL NO. EL 162822485

CLAIMS

1. A compound represented by formula I:



I

or a therapeutically acceptable salt thereof, wherein

X is carbon or nitrogen;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, wherein at least one of R^1 and R^2 is methyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, or R^3 and R^4 may be taken together to form a carbonyl group; and

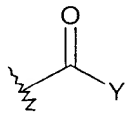
R^5 and R^6 are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl;

with the provisos:

when X is carbon, then R^7 and R^8 are both hydrogen and at least one of R^1, R^2, R^3, and R^4 is hydroxy;

when X is carbon and R^5 is para-halo, then at least one of R^6, R^3, and R^4 is not hydrogen;

when X is nitrogen, then R^8 is not present and R^7 is hydrogen or a group of the formula:



wherein, Y is $-CH_2-NH_2$ or $-NH-CH_3$; and

when X is nitrogen and R^7 is H, then R^3 and R^4 are taken together to form a carbonyl group.

2. The compound represented by formula I of claim 1, wherein the X is carbon.

3. The compound represented by formula I of claim 1, wherein the X is nitrogen.

4. The compound according to claim 2, wherein the compound exhibits an aggrecanase IC_{50} of less than about 20 nM, said aggrecanase IC_{50} measured by an aggrecanase chondrocyte assay.

5. The compound according to claim 4, wherein the aggrecanase IC_{50} is less than about 10 nM.

6. The compound according to claim 4, wherein the compound exhibits a collagenase-1 IC_{50} of greater than about 200 nM, said collagenase-1 IC_{50} measured by a recombinant collagenase-1 assay.

7. The compound according to claim 6, wherein the collagenase-1 IC_{50} is greater than about 1000nM.

8. The compound according to claim 6, wherein the compound exhibits a collagenase-3 IC_{50} of less than about 20 nM, said collagenase-3 IC_{50} measured by a recombinant collagenase-3 assay.

9. The compound according to claim 8, wherein the collagenase-3 IC_{50} is less than about 10 nM.

10. The compound according to claim 8, wherein the compound exhibits a TACE IC_{50} of less than about 40 μM, said TACE IC_{50} measured by a TACE whole blood assay.

11. The compound according to claim 10, wherein the TACE IC_{50} is less than about 10 μM.

12. The compound according to claim 8, wherein the compound exhibits a TACE IC_{50} of greater than about 40 μM, said TACE IC_{50} measured by a TACE whole blood assay.

13. The compound according to claim 1, wherein the compound is selected from the group consisting of:

(2*R*,3*R*) 1-[4-(2,4-dichloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2,4-dichloro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 1-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-4-aminoacetyl-3-methyl-piperazine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-methyl-5-oxo-piperazine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 4-[4-(2-ethyl-benzyloxy)-benzenesulfonyl]-3-methyl-4-carboxylic acid methylamide-piperazine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine- 2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 4-[4-(5-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-methyl-4-carboxylic acid methylamide-piperazine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-fluoro-4-chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(4-fluoro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 1-[4-(2-methyl-5-fluoro-benzyloxy)-benzenesulfonyl]-3-methyl-5-oxo-piperazine-2-carboxylic acid hydroxyamide;

(2*R*,3*S*) 1-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2-methyl-3-fluoro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-chloro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-methyl-3-fluorobenzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2-methyl-5-chloro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2,4-difluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2-fluoro-5-chloro-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,3*R*) 1-[4-(2-methyl-5-fluorobenzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

(2*R*,5*R*) 1-[4-(2-bromo-benzyloxy)-benzenesulfonyl]-5-hydroxy-3,3-dimethyl-piperidine-2-carboxylic acid hydroxyamide; and

(2*R*,3*S*) 4-[4-(2,4-difluoro-benzyloxy)-benzenesulfonyl]-3-methyl-4-carboxylic acid methylamide-piperazine-2-carboxylic acid hydroxyamide.

14. A method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a compound according to claim 1, or a therapeutically acceptable salt thereof.

15. The method for treating a condition selected from the group consisting of osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, corneal scarring, scleritis, AIDS, sepsis and septic shock, comprising administering to a subject in need of such treatment, a therapeutically effective amount of a compound according to claim 1, or a therapeutically acceptable salt thereof.

16. A method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having, said condition a therapeutically effective amount of a small molecule, wherein the small molecule exhibits an aggrecanase IC_{50} of less than about 20 nM, said aggrecanase IC_{50} measured by an aggrecanase chondrocyte assay.

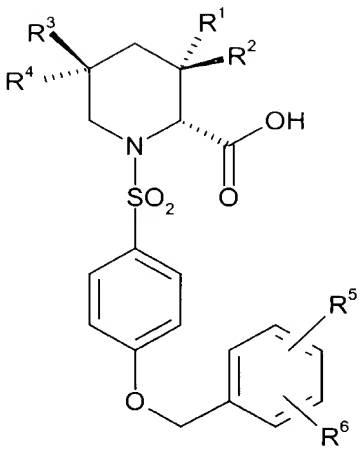
17. The method according to claim 16, wherein the aggrecanase IC_{50} is less than about 10 nM.

18. The method according to claim 16, wherein the small molecule exhibits a collagenase-1 IC_{50} of greater than about 200 nM, said collagenase-1 IC_{50} measured by a recombinant collagenase-1 assay.

19. The method according to claim 18, wherein the small molecule exhibits a collagenase-3 IC_{50} of less than about 20 nM, said collagenase-3 IC_{50} measured by a recombinant collagenase-3 assay.

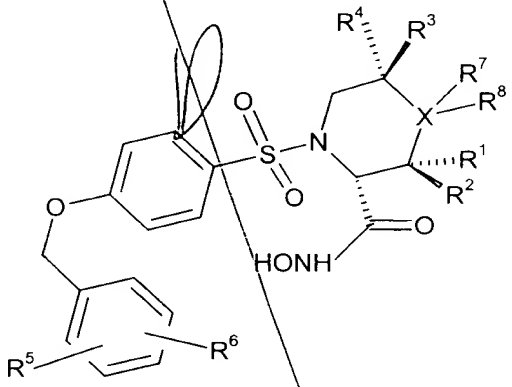
20. The method according to claim 19, wherein the small molecule exhibits a TACE IC_{50} of less than about 40 μM, said TACE IC_{50} measured by a TACE whole blood assay.

21. A compound represented by the formula:



wherein R^1, R^2, R^3, and R^4 are selected from the group consisting of hydrogen, hydroxy, and methyl and R^5 and R^6 are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl.

22. A pharmaceutical composition which comprises an amount effective to treat a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject of a compound of formula I below:



or a therapeutically acceptable salt thereof, wherein

X is carbon or nitrogen;

R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, wherein at least one of R^1 and R^2 is methyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, or R^3 and R^4 may be taken together to form a carbonyl group; and

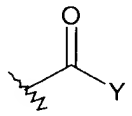
R^5 and R^6 are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl;

with the provisos:

when X is carbon, then R^7 and R^8 are both hydrogen and at least one of R^1, R^2, R^3, and R^4 is hydroxy;

when X is carbon and R^5 is para-halo, then at least one of R^6, R^3, and R^4 is not hydrogen;

when X is nitrogen, then R^8 is not present and R^7 is hydrogen or a group of the formula:



wherein, Y is $-CH_2-NH_2$ or $-NH-CH_3$; and

when X is nitrogen and R^7 is H, then R^3 and R^4 are taken together to form a carbonyl group and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition for the treatment of a condition selected from the group consisting of osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders, autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns, diabetes, corneal scarring, scleritis, AIDS, sepsis and septic shock, in a mammal, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.